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Predictors and Survival Impact of False-Negative Sentinel Nodes in Melanoma

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Abstract

Background—The status of the sentinel lymph node in melanoma is an important prognostic factor. The clinical predictors and implications of false-negative (FN) biopsy remain debatable.

Methods—We compared patients with positive sentinel lymph node biopsy (SNB) [true positive (TP)] and negative SNB with and without regional recurrence [FN, true negative (TN)] from our prospective institutional database.

Results—Among 2986 patients (84 FN, 494 TP, and 2408 TN; median follow-up 93 months), the incidence of FN-SNB was 2.8 %. While calculated FN rate was 14.5 % [84 FN/(494 TP + 84 FN) × 100], when we accounted for local/in-transit recurrence (LITR) this rate was 8.5 % [46 FN/(494 TP + 46 FN) × 100 %]. On multivariate analysis, male gender (OR 2.0, 95 % CI 1.1–3.6, $p = 0.018$), head/neck primaries (OR 2.5, 95 % CI 1.3–4.8, $p < 0.006$), and LITR (OR 3.5, 95 % CI 2.1–5.8, $p < 0.001$) were associated with FN-SNB. Melanoma-specific survival (MSS) for the FN group was similar to the TP group at 5 years (68 vs. 73 %, $p = 0.539$). However, MSS declined more for the FN group with a longer follow up and was significantly worse at 10 years (44 vs. 64 %, $p < 0.001$). On multivariate analysis, FN-SNB was a significant predictor of worse MSS in melanomas < 4 mm in Breslow thickness (HR 1.6; 95 % CI 1.1–2.5, $p = 0.021$).

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Conclusions—Male gender, LITR, and head and neck tumors were associated with FN-SNB. FN-SNB was an independent predictor of worse MSS in melanomas <4 mm in thickness, but this survival difference did not become apparent until after 5 years of follow-up.

Sentinel lymph node biopsy (SNB) has been validated by the Multicenter Selective Lymphadenectomy Trial (MSLT-1) as an important prognostic tool for the management of melanoma.¹ Since its introduction by Morton et al. in 1990, SNB has become the staging procedure of choice for patients with clinically uninvolved lymph nodes whose tumor is 1 mm in Breslow thickness.²

Despite the great utility and reported accuracy of SNB, false-negative (FN) results occur ranging from 2 to 15 % in the literature.^{3–9} Studies have found that multiple variables contribute to FN SNB, including biological and technical factors.^{6,10–12}

While prior research has primarily attempted to identify clinical factors associated with the occurrence of FN-SNB, the impact of FN-SNB on survival outcome has been controversial.^{1,5,8,13–15} The purpose of this study was to identify factors associated with occurrence of FN-SNB in melanoma patients and to determine its impact on survival.

METHODS

This review of prospectively collected institutional database was performed with institutional review board exemption. Patients who underwent successful SNB for cutaneous melanoma at the John Wayne Cancer Institute (JWCI) from January of 1991 to June of 2013 with available follow-up data were analyzed. Factors, including age, gender, primary tumor site, SNB site, tumor characteristics, results of the SNB, recurrence, and melanoma-specific survival (MSS) data, were analyzed. Standard follow-up included visits every 3–6 months for the first 3 years and every 6–12 months thereafter. Adjuvant therapy and follow-up testing were performed at the discretion of the treating physician.

Our technique for SNB has been previously reported in detail.^{6,16–19} In brief, Vital blue dye (1–1.5 mL of 1 % Lymphazurin) was administered 5–15 min before incision, whereas preoperative lymphoscintigraphy was performed 1–4 h before the operation. Sentinel lymph nodes (SN) were defined as lymph nodes that were blue or had evidence of blue channels entering the lymph node. Additionally, radioactive lymph nodes that had count 10 % of the most radioactive nodes or clinically suspicious lymph nodes also were considered as SNs. The majority of the cases (87.4 %, $n = 2623$) in this study were performed with both blue dye and radioactive tracer (99mTc-labeled sulfur colloid) utilizing the hand-held gamma probe, whereas 12 % ($n = 359$) of the cases were performed with blue dye alone. Histopathological analysis of the SN consisted of sectioning and staining with hematoxylin and eosin (H&E) as well as immunohistochemistry with antibodies including S100, HMB-45, and MART-1.

FN SNB was defined as negative SNB with recurrence in the previously sampled lymph node basin. True-negative (TN) SNB was defined as negative SNB without regional recurrence in the previously sampled lymph node basin, whereas true-positive (TP) SNB was defined as SNB with tumor cells found in the lymph node. Patients with positive SNB

were advised to undergo completion lymph node dissection (CLND) when feasible and patients with FN SNB were advised to undergo CLND at the time of the regional recurrence.

Univariate comparisons of clinicopathologic factors among the three groups were performed using χ^2 test or Student's *t* test as appropriate. Survival analyses were performed by constructing Kaplan–Meier survival curves and using log-rank tests. Factors associated with occurrence of FN-SNB status were identified by performing multivariate logistic regression. Additionally, Cox multivariate models were constructed to generate hazard ratios associated with worse MSS. All statistical analyses were performed on SAS version 9.3 (SAS Institute, Carey, NC), and *p* values <0.05 were considered significant.

RESULTS

Overall Demographics

We studied 2986 patients with median follow-up of 93 months. The mean age of the cohort was 56 years, and the median and the mean Breslow depths were 1.2 and 1.8 mm, respectively. The majority of the patients were male (61.0 %) and had Clark level IV–V tumors (51.4 %), whereas trunk (38.7 %) was the most common site of primary tumor. The clinicopathological features of the overall patient population are found in the Supplementary materials (Table S1).

There were 2408 (80.6 %) patients in the TN group and 494 (16.5 %) in the TP group. Eighty-four patients had tumor recurrence in the same nodal basin after a negative SNB correlating to an overall FN incidence of 2.8 %. The calculated FN rate for the study was 14.5 % [84 FN/(494 TP + 84 FN) $\times$ 100 %]. Among FN patients, 38 (45.2 %) also had local/in-transit recurrence (LITR). Because in-basin LITR may also explain FN-SNB, we examined the rate of FN excluding LITR patients; this was 8.5 % [46 FN/(494 TP + 46 FN) $\times$ 100 %]. The median number of excised sentinel nodes was two for all three groups.

FN Group Compared with the TP and TN Groups

We compared the characteristics of the FN patients to those of the TN and TP groups. As expected, compared with TN, FN patients were more male predominant with thicker tumors and more often from the head and neck, most consistent with features predicting nodal metastasis in general. In contrast, relative to TP, FN patients were more male predominant and more head and neck but did not have significantly increased thickness and only trended toward more ulceration. This suggests these features are specifically associated with FN rather than nodal metastasis in general (Table 1).

Predictors of False-Negative Sentinel Lymph Node

On multivariate analysis of preoperative factors, head and neck primary tumor site was the highest independent predictor of FN-SNB (OR 3.2, 95 % CI 1.7–5.9, *p* < 0.001). Other significant factors predictive of FN-SNB were lower extremity primary tumor site (OR 2.3, 95 % CI 1.2–4.5, *p* = 0.001), and male gender (OR 2.1, 95 % CI 1.2–3.7, *p* = 0.011).

Although LITR is not known preoperatively, when LITR was included in our multivariable model, it emerged as the most significant factor associated with occurrence of FN-SNB (OR

3.5, 95 % CI 2.1–5.8, $p < 0.001$). Head and neck primary tumor site (OR 2.5, 95 % CI 1.3–4.8, $p = 0.006$) and male gender (OR 2.0, 95 % CI 1.1–3.6, $p = 0.018$) remained significant predictors of FN-SNB.

Because LITR is a biological factor, we also performed an analysis excluding all patients in our cohort with LITR to highlight *technical* factors associated with FN-SNB. On such analysis, we found that head and neck primary tumor site (OR 4.6, 95 % CI 1.7–12.7, $p = 0.003$) and the use of blue dye alone (OR 3.4, 95 % CI 1.3–8.8, $p = 0.014$) were significantly associated with the occurrence of FN-SNB. The rate of FN (excluding LITR) varied among surgeon between 2.3 and 25 %. On multivariable analysis, however, only one surgeon's FN rate was significantly above others.

Recurrence Patterns

Significantly higher proportion of patients in the FN group experienced LITR compared with the other groups. At median follow-up of 93 months for the entire cohort, there were 38 LITR (45.2 %) in the FN group compared with 83 (16.8 %) in the TP and 85 (3.5 %) in the TN group ($p < 0.001$). The median time to occurrence of LITR in the FN group was 38 months compared to 56 months for the TP group, and 96 months for the TN patients (Fig. S1 Supplementary materials).

By definition, all patients in the FN group experienced regional recurrence. The median time to the occurrence of nodal failure in the FN group was 22.5 months. Conversely by definition, no patient in the TN group had regional nodal recurrence. In the TP group, there were 43 (8.7 %) regional recurrences during the study period with median time to recurrence of 65 months (Fig. S2 Supplementary materials).

The rate of distant metastasis was significantly higher in the FN group compared with the TP and the TN group. With median follow-up of 93 months, 61.9 % (52) of the patients in the FN group experienced distant metastasis compared with 31.8 % (157) in the TP group and 7.6 % (184) in the TN group ($p < 0.001$). In the FN group, median time to distant recurrence was 46 months. Median time to distant metastasis was 96 months for the TN group and 61 months for the TP group (Fig. S3 Supplementary materials).

Survival Analysis

The 5- and 10-year MSS for the entire cohort was 91 and 86 %. The 5-year MSS was similar between the FN group and the TP group (67.8 vs. 72.5 %, $p = 0.539$). However, 10-year MSS was significantly worse for the FN group compared with the TP group (43.5 vs. 64.0 %, $p = 0.007$). The TN group had significantly better MSS compared with both the TP and the FN groups with 5- and 10-year MSS of 95.7, and 92.1 % (Fig. 1).

In patients with melanoma <4 mm in thickness ($N = 2626$), the 5- and 10-year MSS were 93.2 and 88.4 %. FN group had similar 5-year MSS compared to the TP group (70.8 vs. 77.3 %, $p = 0.349$). However, FN group had a significantly worse 10-year MSS compared with the TP group (44.8 vs. 68.8 %, $p = 0.003$). The TN group had significantly better MSS compared with the other two groups with 5- and 10-year MSS of 96.5 and 93.3 % ($p < 0.001$; Fig. 2).

For patients with melanoma ≤ 4 mm in thickness ($N = 267$), 5- and 10-year MSS were 71.0 and 61.0 %. The FN group had similar MSS compared with the TP group at 5 (57.0 vs. 56.6 %, $p = 0.812$) and 10 years (36.7 vs 48.0 %, $p = 0.612$). The TN group had significantly better MSS compared to the other two groups with 5- and 10-year MSS of 82.7 and 73.5 % ($p < 0.001$; Fig. 3).

On multivariate analysis of preoperative factors, the following were associated with worse MSS: age > 65 years, ulcerated primaries, cervical SNB site, and Clark level IV–V tumors. Breslow thickness was associated with worse survival in the TP and the TN group (Table S2, found in the Supplementary materials). FN-SNB was not associated with worse MSS in the overall cohort (HR 1.4, 95 % CI 1.0–2.0, $p = 0.079$); however, for patients with melanoma < 4 mm in thickness ($N = 2626$), FN-SNB was an independent risk factor for significantly worse MSS (HR 1.6, 95 % CI 1.1–2.5, $p = 0.021$). In patients with melanoma ≤ 4 mm in thickness, FN-SNB was not independently associated with worse MSS (HR 1.0, 95 % CI 0.5–2, $p = 0.925$; Table 2).

DISCUSSION

Although sentinel node biopsy has substantially improved the accuracy of nodal staging in melanoma, FN biopsies are a real concern.²⁰ Nodal recurrence after a negative sentinel node biopsy negates not only the staging value of the test but also any therapeutic benefit from early nodal treatment. The causes and complete implications of FN-SNB have not been fully elucidated. We undertook this study, which to our knowledge is the largest such study to date, to examine not only the factors that are associated with FN-SNB but also the clinical implications of their occurrence.

Our study demonstrates that FN-SNB is associated with head and neck primary tumor sites and male gender. In addition, we found that LITR is very strongly associated with FN-SNB. It is important to note that our study is aided by long-term follow-up (median 93 months) and a fairly robust sample size. Because nodal recurrence is a time-dependent phenomenon, longer follow-up reduces the risk that factors related to *early* recurrence are falsely discovered rather than those related to the overall risk of FN. Indeed, our study did not find that tumor thickness was related to FN-SNB, as had been indicated in some other studies.^{5,8,14} While thickness is clearly related to nodal metastasis, it does not appear to be related to FN-SNB.

The correlation of LITR to FN-SNB is intuitive, given the demonstrated presence of tumor cells in extranodal lymphatic sites among those patients. However, the strength of this association was surprising with more than 40 % of FN-SNB associated with LITR. This suggests that the cause of many FN-SNB is not a technical failure of the procedure, but a biological phenomenon where tumor cells arrive at the lymph node after the biopsy has been performed. In practical terms, it implies that clinicians should be wary of the possibility of nodal recurrence in patients who have LITR, even if a prior SNB was negative. Repeat SNB at the time of LITR should also be considered.²¹

The increased rate of FN-SNB in the head and neck region may be related to technical factors, including the complex drainage patterns of that region.^{22–24} However, we did not initially find an association of other technical variables with FN-SNB. Because the dominant association of LITR to FN-SNB might obscure technical variables, we performed a separate analysis excluding that population, and in that analysis, technical factors emerged as significant. These include an improvement in the rate of FN with the use of combination tracers rather than blue dye alone. In addition, FN rates varied considerably by surgeon, although this was only statistically significant for one. So while LITR is a likely biological cause of FN-SNB, accurate technical performance of the test remains critically important.

The relationship of gender to FN-SNB is curious and currently unexplained. While it is well known that male gender is an adverse prognostic factor in melanoma, it is not clear why this would be related to the accuracy of lymphatic mapping. However, ours is not the first study to identify this relationship, so further investigation may be indicated to examine the role of gender in lymphatic function and metastasis.^{15,25–27}

The other major issue examined in this study is the impact of FN-SNB on outcome. Prior reports regarding any adverse effect on survival caused by a missed sentinel node metastasis have been mixed, particularly when comparing true positive (TP) patients to FN patients. Scoggins et al. reported better outcomes for TP patients (62.3 vs. 52.8 % 5-year survival, $p = 0.319$) but not to a statistically significant degree.⁸ Caraco et al. reported that there was an adverse survival impact of FN-SNB relative to true-positive SNB, which was significant, but took several years to develop.¹³ Two other retrospective series did not show a significant disadvantage to FN-SNB, but both were limited by relatively short follow-up (36 and 44 months).^{5,14} Indeed, in our study, when analyzed with 5 years of followup, there was no significant difference between TPs and FN. However, separation of FN and TP survival increased with time after 5 years becoming both clinically and statistically significant.

There also was a meaningful relationship between tumor thickness and the survival impact of FN-SNB. This is consistent with earlier data that suggested that for patients with thick melanomas, the timing of any nodal intervention was not important for survival.^{1,28} For patients with intermediate-thickness melanoma, however, earlier treatment of nodal disease appear to impart a significant survival advantage. Among patients with thick primary melanomas there was no decrease in survival for FN-SNB. With tumors <4 mm in thickness, there was a significant advantage for true-positive patients who had early lymph node treatment compared with patients with FN-SNB.

CONCLUSIONS

Male gender, LITR, and head and neck primary tumors were associated with FN-SNB. Patients with FN-SNB had higher rate of distant metastasis and regional recurrences compared with those who had tumors detected during their SNB and those who had negative SNB. Furthermore, FN-SNB was an independent predictor of worse MSS in melanomas <4 mm in thickness, but this survival difference did not become apparent until after 5 years of follow-up. This may indicate that any possible benefit of completion node dissection in SNB metastasis patients may require extended follow-up to identify.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.
MSS melanoma-specific survival, comparing the *FN* false-negative, *TP* true-positive, and *TN* true-negative groups

FIG. 2. *MSS* melanoma-specific survival, comparing the *FN* false-negative, *TP* true-positive, and *TN* true-negative groups for patients with melanoma <4 mm

FIG. 3. *MSS* melanoma-specific survival, comparing the *FN* false-negative, *TP* true-positive, and *TN* true-negative groups for patients with melanoma ≤ 4 mm

TABLE 1
Comparison of demographics and tumor characteristics between false-negative (FN), true-negative (TN), and true-positive (TP) groups

Characteristics	False-negative (FN) Group (N = 84)	True-negative (TN) Group (N = 2408)	True-positive (TP) Group (N = 494)	P value (χ^2 test)	
				FN versus TN	FN versus TP
Age, years (range)	59.3 $\pm$ 14.1 (24.8–85.8)	56.4 $\pm$ 16.5 (8.0–99.8)	53.9 $\pm$ 18.2 (4.0–98.7)		
<65	53 (63.1 %)	1615 (67.1 %)	340 (68.8 %)	0.447	0.298
65	31 (36.9 %)	793 (32.9 %)	154 (31.2 %)		
Gender					
Female	20 (23.8 %)	949 (39.4 %)	196 (39.7 %)	0.004	0.006
Male	64 (76.2 %)	1459 (60.6 %)	298 (60.3 %)		
Primary site					
Arm	10 (11.9 %)	501 (20.8 %)	70 (14.2 %)	<0.001	<0.001
Leg	25 (29.8 %)	470 (19.5 %)	136 (27.5 %)		
Head/neck	29 (34.5 %)	503 (20.9 %)	85 (17.2 %)		
Trunk	20 (23.8 %)	934 (38.8 %)	203 (41.1 %)		
Breslow depth, mm (range)	2.9 $\pm$ 2.7 (0.1–17.0)	1.5 $\pm$ 1.5 (0.7–18.0)	3.0 $\pm$ 3.3 (0.4–55.5)	<0.001	0.458
<1	12 (14.3 %)	1086 (45.1 %)	53 (10.7 %)		
1–3.99	51 (60.7 %)	1096 (45.5 %)	328 (66.4 %)		
4	18 (21.4 %)	144 (6.0 %)	105 (21.3 %)		
Unknown	3 (3.6 %)	82 (3.4 %)	8 (1.6 %)		
Ulceration					
Yes	27 (32.1 %)	328 (13.6 %)	141 (28.5 %)	<0.001	0.055
No	50 (59.5 %)	1993 (82.8 %)	337 (68.2 %)		
Unknown	7 (8.3 %)	87 (3.6 %)	16 (3.2 %)		
Clark level					
I–II	2 (2.4 %)	447 (18.6 %)	17 (3.4 %)	<0.001	0.652
III	18 (21.4 %)	777 (32.3 %)	81 (16.3 %)		
IV	50 (59.5 %)	1005 (41.7 %)	323 (65.5 %)		
V	9 (10.7 %)	94 (3.9 %)	54 (10.9 %)		
Unknown	5 (6.0 %)	85 (3.5 %)	19 (3.9 %)		
SNB sites					

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Characteristics	False-negative (FN) Group (N = 84)	True-negative (TN) Group (N = 2408)	True-positive (TP) Group (N = 494)	P value (χ^2 test)	
				FN versus TN	FN versus TP
Cervical	33 (39.3 %)	629 (26.1 %)	104 (21.1 %)	0.006	0.004
Axillary	26 (30.9 %)	1179 (49.0 %)	212 (42.9 %)		
Inguinal	25 (29.8 %)	578 (24.0 %)	177 (35.8 %)		
Other	0 (0 %)	22 (0.9 %)	1 (0.2 %)		

SNB sentinel lymph node biopsy

TABLE 2

Cox proportional hazard ratio of clinicopathologic factors associated with worse melanoma specific survival stratified by Breslow depth

	Hazard ratio	95 % CI	P value
Melanoma <4 mm (<i>N</i> = 2626)			
Age (years)			
<65	Referent		
65	1.9	1.5–2.5	<0.001
SNB site			
Axillary nodal basin	Referent		
Cervical nodal basin	2.2	1.4–3.6	0.001
Inguinal nodal basin	1.1	0.7–1.9	0.699
Sentinel LN status			
True-positive	Referent		
True-negative	0.2	0.2–0.3	<0.001
False-negative	1.6	1.1–2.5	0.021
Ulceration			
No	Referent		
Yes	2.3	1.8–3.1	<0.001
Clark level			
I–III	Referent		
VI–V	2.2	1.6–2.9	<0.001
Primary tumor site			
Upper extremity	Referent		
Head and neck	0.9	0.5–1.6	0.661
Trunk	1.5	1.0–2.4	0.045
Lower extremity	1.4	0.7–2.7	0.360
Melanoma ≥ 4 mm (<i>N</i> = 267)			
Age (years)			
<65	Referent		
65	1.8	1.2–2.8	0.008
Sentinel LN status			
True-positive	Referent		
True-negative	0.3	0.2–0.5	<0.001
False-negative	1.0	0.5–2.1	0.925
Ulceration			
No	Referent		
Yes	1.2	0.8–1.9	0.399